ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

1957

243 CHARLES STREET

BOSTON, MASSACHUSETTS

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THE time of the Annual Report is an occasion for stock-taking and policy review. It is a time to ask not only what has been done (or not done) but where we are going and how. The Howe Laboratory is a unit occupying approximately 4,500 square feet having an operative staff of, usually, a half dozen career investigators and an equal number of transient investigators engaged primarily in a study of the eye and its diseases. It has a uniquely favorable liaison with an active clinical hospital and it enjoys the moral and financial support of a host of friends. The aim of the Howe Laboratory is to elucidate and report on various biologic processes involving the eye and to lay the groundwork for an understanding of eye diseases. It falls frustratingly short of accomplishing all that is hoped of it.

To bring the techniques of modern science to bear on problems of the eye is to bring basic scientists into the Laboratory. It is no longer possible for one person to encompass the multi-faceted techniques which are now available to the scientific investigator and at the same time to have an intimate knowledge of clinical disease. How many ophthalmologists, for instance, are skilled in the techniques of electrophoresis, chromatography, strain gages, or electronic amplification? Yet these are standard techniques of biologic laboratories. Contrariwise where is the basic scientist who, though familiar with these techniques, has the experience and judgment necessary to deal with diseases of the eye and with patients? The unfortunate truth is, of course, that such paragons are vanishing with the accelerated development of scientific methodology. The solution must depend on teamwork where basic and clinical scientists are brought together for combined attacks on problems of mutual interest. To this end the Howe Laboratory attempts to provide a meetinghouse and facilities for those whose talents may most profitably contribute to ophthalmic research. The following paragraphs record some of the fruits of this conjugation of interest for the year nineteen hundred and fifty-seven.

Research Activities

Ocular hydrodynamics and glaucoma

The fact that glaucoma is one of the principal causes of blindness in this country is in itself an adequate reason for

concentrating the research efforts of one department, under the supervision of Dr. Grant, upon the causes and treatment of this disease. An additional and particularly strong impetus to this research has been provided by the great personal interest and enthusiasm which Dr. Paul Chandler shares with us in this study. Most of the work on ocular hydrodynamics which is carried on in this laboratory is very closely related to clinical problems of glaucoma, and Dr. Chandler almost daily discusses with us the results and aims of these experiments. This has mutual advantages, for he sees in our experimental findings what there is of value for immediate application in the treatment of patients, while we gain greatly from his counsel and guidance based on vast clinical experience. We are further indebted to Dr. Chandler for the fact that he has provided the opportunity for one of us to assist him frequently in the operating room in the evolution of improvements in surgery for glaucoma, and thus to share with him the excitement and satisfaction of his practical achievements.

During the years that glaucoma has been studied in the Howe Laboratory we have advanced by definite stages in our understanding of the disease. Work in the Howe Laboratory has contributed significantly to these advances. In the nineteen thirties and much earlier the intraocular pressure in glaucoma was known to be abnormally high, and damage to the optic nerve with loss of vision was the recognized result. By the early nineteen forties strong evidence was obtained that a secretory process supplied part of the intraocular fluid and could hypothetically provide at least the osmotic potential necessary for considerable elevation of intraocular pressure. By the early fifties it was established that in almost all types of glaucoma obstruction of the channels through which intraocular fluid normally escapes from the eye, rather than an excess formation of this fluid, is responsible for the abnormally high intraocular pressure in glaucoma. At the same time the different kinds of glaucoma were more clearly differentiated from one another, and one type (angle-closure glaucoma) was proven to be readily curable by a safe and reliable surgical procedure. Since then new drugs for the reduction of intraocular pressure have been discovered. However, as yet, the cause of the majority of cases of glaucoma remains unknown, and treatment of the majority, while very helpful, is not curative.

At present, interest focuses most strongly, among those concerned with research on glaucoma, upon the minute channels through which the intraocular fluid flows out of the eye, for we now know that in most cases of glaucoma it is some abnormality of these channels which is responsible for damming back the fluid in the eye and thereby raising the intraocular pressure. Careful study of the character and properties of these channels in normal eyes is, of course, a prerequisite to recognizing what is wrong with them in glaucomatous eyes. Studies utilizing various techniques for investigating in patients' eyes the pressure, the rate of flow and the facility of outflow of intraocular fluid under various conditions have been and continue to be highly informative, but to get down to the fine details of examining the hydrodynamic properties of so small a part of the eye as the outflow channels themselves, it becomes almost essential to have recourse to eyes which have been left to the Eye Bank for research.

Techniques which have been developed in the Howe Laboratory in recent years for analyzing the hydrodynamic properties of enucleated human eyes have been utilized in the past year for study of the tissue containing the innermost portion of the outflow channels, the trabecular meshwork. Principally by microdissection of this meshwork and by examining the influence of experimentally induced tensions in this meshwork on the facility of flow of fluid through it, it has been possible to establish that this tissue is responsible for approximately 75 per cent of the resistance to flow which controls the pressure in normal eyes. Furthermore, it has been found that forces transmitted from the ciliary muscle and iris to the trabecular meshwork are effective in varying the facility of flow through this tissue. This probably forms one basis for the action of certain eye drops, such as pilocarpine, which are used in treatment of glaucoma; these drops cause contraction of muscle in the ciliary body and iris, which in turn acts upon the trabecular meshwork to improve facility of outflow of intraocular fluid and thereby allow the intraocular pressure to become lower. It remains now to be determined whether in glaucomatous eyes the channels in the trabecular meshwork or the more peripheral channels in the sclera offer the abnormally great resistance to flow responsible for the elevated intraocular pressure. Observations on the actions of drugs suggest that the trabecular meshwork is the principal site of abnormality.

The findings of the past year have definite implications concerning treatment for glaucoma. Opening or removing the trabecular meshwork in enucleated normal human eyes has been found significantly to decrease the resistance to outflow of fluid from the eye. This procedure might be expected to benefit glaucomatous eyes, particularly if the trabecular meshwork proves to be the site of the abnormal resistance characteristic of this disease as well as the site of major resistance in the normal.

The laboratory investigations of channels for outflow may most immediately relate to the clinical problem of congenital glaucoma which Drs. Chandler and Grant have been studying together clinically. This condition has a number of controversial aspects, and the experimental study of effects of opening the trabecular meshwork suggest an explanation for some of the results which have been obtained in treating this type of glaucoma surgically.

Other studies concerning ocular hydrodynamics which have been carried on recently in the Laboratory have been aimed at learning more about the secretion of intraocular fluid. An electrical potential difference has been known to exist between the blood stream and the intraocular fluid, and it has been thought possible that this electrical potential might have some connection with the secretory process. Experiments on rabbit eyes have, however, failed to establish such a connection. It is found that the intraocular pressure and facility of outflow may remain unchanged even when the electrical potential is greatly reduced by administration of poisons. It is inferred that the rate of secretion is not related to the potential. Furthermore, administration of a drug (Diamox) which lowers the rate of formation of intraocular fluid does not alter the electric potential.

While the foregoing studies were being supervised, and largely carried out, by Dr. Grant, related studies on homeostatic mechanisms in the control of intraocular hydrodynamics were being conducted by Dr. Maurice Langham on the rabbit and cat eye. In the dead eye the intraocular pressure was found to increase proportionately, over a wide range, with the rate fluid was delivered to it. In the living eye, on the other hand, evidence was found that, at low infusion rates, there was compensatory decrease in either the rate of formation of the aqueous humor or of the outflow resistance. The maximal

compensation in the living eye corresponded to 30 to 50 per cent of the normal rate of formation or the outflow resistance.

Section of the preganglionic cervical sympathetic nerve was found to abolish the homeostatic response, but ligation of one common carotid artery had no effect.

To study the influence of increased pressure on the rate of aqueous humor formation, an attempt was made to isolate the process of aqueous humor formation from that of drainage. This was achieved by introducing the manometer needle directly into the posterior chamber and replacing the aqueous humor of the anterior chamber by mineral oil to block the drainage vessels. Under these conditions, secretion of aqueous humor led to a rapid increase in the intraocular pressure to approximately 100 mm.Hg., at which level secretion ceased; secretion resumed when the excess aqueous humor was removed. In the physiologic range the increase in volume of the eye was found to decrease exponentially with the pressure.

Further evidence that the rate of formation could be readily modified was found in similar experiments in which the preganglionic cervical sympathetic was stimulated. Stimulation of the nerve caused a reduction in the rate of formation of the aqueous humor. On the other hand section of the nerve or ligation of the common carotid artery did not significantly affect aqueous formation.

In other studies the effect of pressure and other factors on the outflow resistance were studied. An increase in the intraocular pressure was found to cause slow changes in the outflow resistance but the physiological significance of these changes remains to be clarified. Evidence was also found that changes in outflow resistance take place in the period immediately after death or enucleation of the eye.

In a separate study, further attempts have been made to elucidate the role of carbonic anhydrase in the secretion of the aqueous humor. This has been undertaken by Dr. Langham in conjunction with Dr. T. Maren, Professor of Pharmacology at the State University of Florida, Gainesville. In these studies the carbonic anhydrase inhibitor, Diamox, and a new more potent inhibitor was used in varying experimental conditions to test their action on the chemistry and formation of the aqueous humor and the cerebrospinal fluids in the cat. Several aspects of this complicated problem were studied and the results are now being analyzed. It is of interest that the new

inhibitor, Neptazane, was found to reduce the formation of the aqueous humor and the spinal fluid at concentrations below that required by Diamox. Furthermore, reductions in the formation of these fluids occurred without any change in the distribution of bicarbonate between these extracellular fluids and the plasma.

A group of clinical investigations on glaucoma have been under way in the Glaucoma Consultation Service. The Laboratory is connected with these in an advisory manner. Dr. Pei-Fei Lee has been analyzing by means of tonography and gonioscopy the effects of a number of drugs, including chlorothiazide, dichlorphenamide, epinephrine, phenylephrine, and cortisone at high dosage levels.

Biochemistry of the Lens and Cataracts

There are a number of biochemical changes which occur in the cataract process and one of the most prominent of these involves the sulfhydryl (-SH) groups. These groups are found in the lens protein as well as in the non-protein component, glutathione. A study has been undertaken by Dr. Kinoshita and Mr. Merola of the distribution of these sulfhydryl groups and the possible relationship to the different types of protein normally found in lens. Since many of the changes observed in cataract formation are similar to those found in the normal aging process of the lens a comparison of the sulfhydryl and protein content was also made in lenses of calves and cattle.

It has been known for some time that the glutathione concentration in lens is higher than that observed for any other tissue. This fact became even more interesting when it was discovered that the glutathione in the cortex of the lens is almost five times that of the nucleus. The explanation for the concentration of this tripeptide in the cortex is not as yet completely understood. It is probable, however, that glutathione is both synthesized and bound in some way in this part of the lens. Despite this high concentration of glutathione, the protein sulfhydryl content is lower in the cortex than in the nucleus. In fact, there appears to be a close reciprocal relationship between the cortex and nucleus in regard to the distribution of glutathione and protein sulfhydryl groups.

In comparing young with old lenses it appears that the protein sulfhydryl groups of the calf lens is much higher than that of the cattle lens. An explanation for this difference seems

to be that in the calf lens the alpha crystallin, the lens protein with a low -SH content, is not present in as high a concentration as is found in the cattle lens. The majority of the calf lens proteins is made up of the beta and gamma crystallins and these are proteins rich in the -SH content.

Before it is possible to understand the causes of cataract formation, it is essential to know more about the basic processes existing in the normal lens. One such basic process studied was the means by which the lens utilizes glucose and converts it to lactic acid and carbon dioxide. It is worth noting in this regard the advantages of the close collaboration between two different ophthalmic research laboratories. Drs. Wachtl and Kinsey at the Kresge Eye Institute have been developing and improving the method of maintaining the lens outside the eye in a synthetic medium for long periods of time, while in the Howe Laboratory Dr. Kinoshita and Mr. Merola have developed the isotopic approach to glucose metabolism and the isolation of metabolic products from the lens. By combining the efforts of these two laboratories a great deal of information has been acquired about the complex pattern of the lens glucose metabolism.

Fat Formation in the Eye and Other Tissues

The results of some five years of intensive investigation on a type of fat formation, involving more than a thousand separate experiments, have now been published in a series of three articles in the Archives of Pathology under the general title of Aberrant Lipogenesis. These studies sponsored initially by a small grant from the Eye Bank and later by annual grants from the Massachusetts and American Heart Associations have run an interesting and unpredicted course. They were begun by Dr. Cogan with what seemed to be a simple investigation of the significance of that fatty ring, called arcus senilis, which is a common accompaniment of age. Soon these studies were directed toward an investigation of the mechanism by which the cornea and the eye handled fat. The study assumed major proportions as Dr. Kuwabara joined the staff, and resulted in the exciting and wholly unanticipated discovery that of all substrates oleic acid was the essential constituent for lipogenesis in corneal cells. When a technique was developed to induce aberrant lipogenesis in the test-tube as well as in the intact animal it became evident that two further essential elements

were necessary: first, the presence of serum and secondly, intact cells containing a lipogenic enzyme.

A lengthy series of experiments were then undertaken, with moderate success, in attempting to elucidate each of these three factors: the substrate factor, the serum factor, and the tissue factor. These are the emphases in the three articles cited. Further experiments are currently directed toward the study of the fat by means of radioactive substrates and by histochemical approach to enzymes in the lipogenic cells. Electron microscopy by Dr. Ikui has indicated that the site of fat formation within the cells appears to be unrelated to the distribution of mitochondria but nevertheless lipogenesis does have a most suggestive correlation with some, at least, of the enzymes operative in carbohydrate metabolism. Obviously the study is far from complete.

The significance of these investigations is clearly not limited to the eye. In fact, the phenomenon of aberrant lipogenesis may be induced in a wide variety of cells. Particularly relevant, of course, is the possibility that these findings apply to the fat formation in atheroma (arteriosclerosis) and to so-called fatty degeneration in general. To this end several lines of investigation are being pursued. The experimental lipogenesis is being compared with the changes that occur natively in the blood vessels of man and with that which may be induced by feeding cholesterol to rabbits. The incidental and suggestive finding that human serum is more lipogenic than animal serum has resulted in a systematic attempt, by Dr. Eugene Ciccarelli, to correlate the lipogenic capacity of serum from various individuals with their degree of arteriosclerosis. These and many other approaches will be followed in the belief that the phenomenon which happened to be observed first in the eye has wide biologic significance.

Toxicology and the Cornea

This project, as previously described in these Annual Reports, is a systematic study of the relationship between the chemical properties of the cornea, studied by Dr. Kern, and the physical changes, such as loss of transparency, which are induced by contact with injurious substances, studied by Dr. Grant. Primarily, this is a study of "chemical burns" of the cornea, with the ultimate aim of improving their treatment. Actually, worth-while improvements in treatment have already

resulted. As a by-product of these studies of chemical action and injurious effect new knowledge is being gained concerning the normal chemical and physical state of the principal components of the cornea.

Studies in this category in previous years concerned the injurious actions of alkalies, metal salts and surface active agents upon the cornea. Among the facts learned from these investigations was that metals generally interact preferentially with the mucoproteins of the cornea. Furthermore, it was found that in most instances in which metal and mucoprotein combine in a readily dissociable manner without rendering the mucoprotein insoluble, no serious change in the physical properties of the cornea results. On the other hand, metals which interact with the cornea to form a poorly dissociable combination commonly make the mucoprotein insoluble and alter the hydration properties of the cornea, ultimately causing opacification of the cornea. This opacification was found to be preventable by timely application of appropriate counteragents which were discovered to remove the metal from its combination with the cornea.

More recently the chemical and toxic effects of dyes upon the cornea have been under investigation, and it has been confirmed that the cationic dyes generally cause corneal opacity, but that the anionic usually do not. The cationic dyes appear to interact with carboxyl groups of the cornea, particularly of the mucoprotein, with an affinity similar to that of the toxic metals. These dyes are found similarly to alter the physical properties of the cornea, particularly the hydration characteristics.

In the course of this study, methods were worked out for chromatographic and electrophoretic purification of dyes, and several were prepared in a purer state than had previously been obtainable. This was done to avoid confusion from contaminants which caused occasional spurious experimental results when commercial dyes were employed. In one instance of incidental interest, these purification procedures served to resolve a mystery concerning a difference in toxicity of American and foreign samples of a dye known as Rose Bengal. A sample of dye by this name was sent from Afghanistan, where it is reported to have caused many cases of blindness when it has been applied to the eye as a home remedy for a variety of ailments. On the other hand, Rose Bengal of American or

European manufacture has been often applied in solution to patients' eyes by ophthalmologists in this country to stain the cornea for diagnostic purposes without causing serious injury. Tests on rabbits showed that the Rose Bengal from Afghanistan caused corneal opacity, while that from America or Europe did not. The underlying difference was revealed when chromatographic and electrophoretic procedures were applied, for these established that the domestic and European material was, as expected, an anionic dye, while the material which caused corneal injury was in fact a cationic dye, despite having the same name. These different dyes did then conform to the generalization already mentioned concerning the innocuous nature of the anionic and injurious character of the cationic dyes.

Optics and Instrumentation

In line with Dr. Donaldson's interests in ophthalmic instrumentation, a new retinal camera which takes simultaneous stereoscopic photographs is now in operation after several years of work. Electronic flash tubes with a duration of 1/1000 second serve as an intense light source and these have been specially designed in cooperation with Dr. Harold Edgerton of Massachusetts Institute of Technology. The important depth relationships of various lesions of the retina can be recorded and the conditions exactly duplicated in subsequent photographs. This type of picture is often of considerable value in tumors of the retina, for example.

Another step in documenting and teaching by visual means has been the development of a stereomovie camera and projector for close-up photography. It is felt that this may be particularly valuable in showing various ophthalmic surgical techniques and a group of surgical procedures are now being recorded for stereomovie projection.

The newer methods of indirect ophthalmoscopy which were so productively developed some years ago by Dr. Schepens while a member of the Howe Laboratory staff, were re-examined this past year by Dr. Donaldson with the aim of developing an instrument which did not invert the retinal image. Such an instrument was developed and tried out clinically. While it may have advantages for those who are first learning indirect ophthalmoscopy, the advantages do not at present seem

sufficient to warrant the additional expenses involved in its manufacture.

Neuro-ophthalmology

The cross fertilization which occurs perennially between the Howe Laboratory and the Department of Neurology has yielded in the past several new and sometimes exciting disclosures. Notable this year has been a conjoint study on the ocular changes in the entity of metachromatic leucoencephalopathy by Drs. Cogan, Kuwabara, and E. P. Richardson (Department of Neuropathology). In this fatal and blinding disease of childhood a peculiar staining quality of the white matter in the brain has naturally directed attention to myelin. We have, however, demonstrated this substance in certain cells of the retina which has no myelin and have thus added to the evidence that the cause of the disease is in large part a primary defect in the cells of the nervous system unassociated with myelin. At present we are pursuing studies directed toward the chemical identification of the characteristic substance which collects in the cells of the retina in this disease and hope that, in some way, our findings may contribute to the ultimate solution of this tragic condition in children.

Also referable to the continuing interest in neuro-ophthalmology was an informal study on some aspects of the vestibulo-ocular system. This was made possible by a personal attack of so-called vestibular neuronitis by one of us and by the opportunity to study in detail two persons who had lost their labyrinths through streptomycin intoxication. The significant conclusion of these observations is that the labyrinth normally exerts a control over the eyes for what might be surprisingly small movements of the head. The sensitivity of this control is generally unappreciated. It is the loss of this delicate control which accounts for much of the dizziness and illusory movement of the environment that follows destruction of the labyrinths.

Last year's Report contained a reference to an apparatus developed largely by Dr. John Gorman with the support of the Society for the Prevention of Blindness for testing the opticokinetic response in infants. It was a surprise to many of us to learn that infants had a considerable measure of vision

and were capable of a well executed opticokinetic response within a few hours after birth. The use of the opticokinetic response for the objective measurement of visual acuity was further developed this past year by Robert Reinecke, a student Fellow who spent several months in the Laboratory under the auspices of the Society to Combat Blindness. The Reinecke apparatus was adapted to the objective measurement of acuity in children with amblyopia and was found to correlate well with the subjective measurement by the standard Snellen charts. Obviously it had especial value in the estimation of acuity in malingerers, hysterics, and in children too young to permit subjective testing.

The data which has been accumulated in the Howe Laboratory during the past five years on retinal diastolic pressure measurements in cases of carotid artery insufficiency are being currently evaluated by Dr. Francis J. West. It appears that the results confirm several reports from other sources that sufficient inequality in the retinal diastolic pressure is a valuable index of carotid artery disease.

Radiation

The studies cited in last year's Report on the ocular effects of microwaves and ultrahigh-frequency radiation have been pursued with accelerated fervor in view of current interest in satellites and guided missiles. Since tracking of these earthly, and unearthly, objects will depend on high energy radar beams, it is most important to predetermine the biologic hazards to military and civilian personnel coming in contact with this type of radiation. Cataracts have been found to be one of the consequences of microwaves in experimental animals and, allegedly, in at least one human being. Because of the potential importance of the ocular effects, Dr. Cogan was appointed chairman of a panel set up to advise the Air Research and Development Command of the Air Force on the biologic effects of microwave irradiation.

The particular interest involving the Howe Laboratory has centered about whole body radiation with a portion of the electromagnetic spectrum in the ultrahigh frequency range (400 megacycles). This is the frequency to be used in Millstone, the powerful new radar installation in the vicinity of Boston, and the present study was carried out with the staff

of Lincoln Laboratory of the Massachusetts Institute of Technology and the Harvard Medical School. Approximately 100 rabbits have been irradiated with lethal and sublethal doses in single and repetitive exposures. Although the animals have been examined periodically for several months after the irradiation, no cataracts have occurred in the surviving animals. It thus appears that under the conditions of these experiments where the entire body was irradiated (in contrast to local irradiation of the eye as has been employed previously) the dose necessary to cause cataracts is more than that which will cause death. Further experiments directed to the ocular effects of this wave band are therefore not contemplated.

Miscellaneous Researches

A study of cystinosis has been cited in these Annual Reports of the past two years. The report of our observations on cystinosis in the adult aroused considerable interest and, properly, scepticism since it was the first and only report of the condition in an adult. Unlike the condition in childhood, this case in the adult appeared to be relatively benign. Because of the scepticism, and with the hope that some useful information might be obtained to indicate why the condition in the adult ran such a different course from that in the child, the patient was again studied. Chromatographic and chemical tests again confirmed the crystals as cystine and, this time, a sternal puncture revealed similar crystals in the bone marrow. Moreover, definitive identification of the crystals as those of cystine was obtained by crystallography through cooperation with Dr. Cornelius Hurlbut of the Department of Mineralogy. While we do not understand why involvement of the kidneys which occurs regularly in childhood cystinosis should be absent in the adult, we have re-established the fact that the crystals obtained from the conjunctiva were those of cystine and that the condition in the adult is a systemic disease.

As the foregoing studies on crystallography were being carried out a coincidence occurred that turned out to be thoroughly profitable, resulting for the first time in the identification of gypsum (calcium sulphate) in an eye. In fact, it is the first time gypsum has been identified in any biologic tissue. The source of the gypsum was a scleral plaque such as is common in elderly persons. Scleral plaques have been one

of the incidental interests of some of us during the past few years and the present case did not appear at first to differ from other cases which we have had occasion to examine. The eye was blind from glaucoma and was removed on account of pain. The area of the plaques was found to be calcific and would not have excited great interest, since calcified plaques of the sclera have previously been described in the literature, had it not been for the crystallographic analysis that indicated almost pure calcium sulphate. This unique finding is all the more surprising since calcification elsewhere in biologic tissue is made up of only a very limited number of compounds, mostly phosphates and carbonates. Whether or not other scleral plaques will be found to contain gypsum remains to be seen. Also, the source of the sulphate needs further investigation.

Another interesting, and confusing, discovery has been that of crystals in the outer portion of some detached retinas. These were actually observed several years ago but for lack of time were not intensively studied until this past year. By microchemical tests of the crystals (laboriously dissected out of the retina) and by crystallography of the involved areas, the crystals have been identified as a mixture of calcium oxalate and calcium phosphate. Although their pathogenesis is totally obscure, they are believed to have considerable significance since oxalate crystals are practically never found elsewhere in tissues of the body and when they do occur in the retina they are found exclusively in its outermost layers. When a preliminary report of these findings was presented in Washington, it was found that, by one of those coincidences which are so common in research, the crystals had been observed and were even then being studied, though by a quite different means, at the Armed Forces Institute of Pathology. Through microincineration this group also came to the conclusion that the crystals were oxalate.

Exploratory studies on the use of human amnion cells in tissue culture for the identification of herpes simplex and adenovirus were undertaken by Dr. and Mrs. Herbert Kaufman while Dr. Kaufman was an intern at the Massachusetts General Hospital. The cytopathogenic changes in the tissue culture developed rapidly and appeared characteristic. All 12 types of adenovirus studied demonstrated similar nuclear changes

in stained preparations. Adenovirus and herpes simplex could easily be distinguished from each other and from non-specific degeneration when stained and unstained cultures were observed. The ease and convenience of virus identification by this method make this procedure an excellent tool for the routine isolation of these viruses which are so important to ophthalmology.

Service Activities

Although primary emphasis is placed on its research function, the Howe Laboratory realizes a considerable responsibility for service functions to the hospital, to the Medical School and to the general medical and scientific community of which it is a part. In one way or another it serves in the operation of the Howe Library, the Department of Ophthalmic Pathology, the Glaucoma Consultation Service and other clinical activities of the Massachusetts Eye and Ear Infirmary as well as in the teaching of undergraduate and postgraduate students of the Harvard Medical School. At the national level it is represented in the Council of Neurological Diseases and Blindness of the Public Health Service, in the Advisory Committee of Ophthalmology of the National Research Council, and in special advisory boards to the armed forces and executive committees of national societies. Time consuming as these activities may be, they are the responsibility of organizations, such as the Howe Laboratory, which aspire to take a lead in this highly specialized field.

A few specific service functions may be noted. The tremendous wealth of teaching material that has been developed through Dr. Donaldson's interest in photography is being made available on a cost basis. Sets of 17 neuro-anatomic slides illustrating the visual pathways together with a descriptive booklet have been distributed to many teaching centers. A second and a larger set of stereophotographs (40 slides) of the chamber angle together with a descriptive booklet is also now available. A demonstration of these and other stereophotographs is being presented monthly by Dr. Donaldson in conjunction with the New England Ophthalmological Society. Also using largely the technique of stereoprojection, an exhibit of ocular complications of diabetes was held this past year at the annual Diabetic Fair of Boston. It was also the privilege of the Howe Laboratory to sponsor a

lecture by Dr. Alan Woods entitled "Immunologic Processes in Diseases of the Eye" presented to the student body of Harvard Medical School and to ophthalmologists.

Perhaps most serviceable is the function which the Howe Laboratory offers as a general clearing house for a multitude of problems centering about the eye. Together with its allied organizations, most particularly the Howe Library, guided by Mr. Charles Snyder, and the Ophthalmic Pathology Laboratory, directed by Dr. Taylor Smith, the Howe Laboratory has been able to offer unique opportunities for many interested in studying problems pertaining to ophthalmology.

Support of the Laboratory

The support of the Laboratory comes from diverse sources and is allocated to diverse ends aiming only to live up to the claim that no equal expenditure of money can bring greater return in research on the eye. The annual income, now amounting to about $40,000 from endowed funds, covers approximately one-half the operating expenses of the Laboratory. For the rest we depend on the benefactions of various agencies and individuals, many of whom have made the Howe Laboratory the object of one of their annual philanthropies. These benefactors are truly part of the team that make the Laboratory possible and deserve much of the credit for whatever success it enjoys.

The government, through its Public Health Service and Atomic Energy Commission, has generously supported project and training facilities in the Laboratory for the past several years and at the same time permitted that freedom in operation of the grants which is so essential for original research. The Massachusetts Eye and Ear Infirmary, which is a sort of foster mother to the Laboratory, provides it with commodious housing, contributes to offsetting its annual deficit, and listens with a sympathetic ear to the Laboratory's perennial request for more space. This past year the Knights Templars made a grant which warrants especial comment not only for its generosity but for the manner in which it was given. Instead of being tied to a specific project, the Knights Templars have given their money for whatever purposes are needed with the decision for its expenditures left to the judgment of those at the operating level. The wisdom of this cannot be overstressed.

Particularly heart warming are the contributions made at the personal level. That various individuals have chosen without solicitation to contribute to the Laboratory is a most gratifying and stimulating event. The Howe Laboratory, although a department of the Harvard Medical School, does not receive income from the general funds of the University. It has no fund raising agency. It has only limited contacts with private patients. What it does have is the good will of a substantial group of friends who have, so far, kept the Laboratory solvent. It is a pleasure, however inadequate, to acknowledge these benevolent contributors to the Laboratory.

For general expenses:

Massachusetts Eye and Ear Infirmary
Knights Templar Eye Foundation, Inc.

Anonymous
William P. Beetham, M.D.
Harry E. Braconier, M.D.
Joseph A. Capps, M.D.
(in memoriam: Edith Ives Cogan)
Richard B. Capps, M.D.
(in memoriam: Edith Ives Cogan)
Sallie C. Carrington
Thomas Cavanaugh, M.D.
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Director

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COGAN, D. G.

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COGAN, D. G.

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The ocular fundus. Postgraduate Course in Cardiology, Massachusetts General Hospital, in Boston, Massachusetts, February 12, 1957.

Nystagmus. Otolaryngology Staff and Residents, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, March 7, 1957.

Comparison of fat deposits in the cornea and blood vessels. New England Cardiovascular Society, in Boston, Massachusetts, March 11, 1957.

Eye pathology. Harvard Medical School, Department of Pathology, in Boston, Massachusetts, March 27 and December 21, 1957.

Oculomotor innervation and its disorders. Harvard Medical School, Departments of Neuropathology and Neurology, in Boston, Massachusetts, April 19, 1957.

Altitudinal hemianopsia. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 23, 1957.

Ocular complications of diabetes. Postgraduate Course in Internal Medicine, Massachusetts General Hospital, in Boston, Massachusetts, June 28, 1957.

Neuro-ophthalmology. Series of lectures and conferences at the University of North Carolina and Duke University, in Durham and Raleigh, North Carolina, September 30–October 4, 1957.

Histochemistry. Series of lectures to the Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 8–26, 1957.

Neuro-ophthalmology. Connecticut Postgraduate Seminar in Psychiatry and Neurology, in New Haven, Connecticut, October 21, 1957.

Nystagmus. Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, November 14, 1957.

Some ocular motor syndromes. New York Academy of Medicine, in New York, New York, November 18, 1957.

House Officer Lectures

Nystagmus. Massachusetts Eye and Ear Infirmary, January 29, 1957.
Systemic diseases in ophthalmology. Massachusetts General Hospital, Department of Internal Medicine, July 19, 1957.

DONALDSON, D. D.

Corneal dystrophies and degenerations. New England Ophthalmological Society, in Boston, Massachusetts, March 20, 1957.

Corneal dystrophy. Series of lectures at University of Kansas, in Kansas City, Kansas, April 10–12, 1957.

Corneal dystrophy. Western Reserve University, in Cleveland, Ohio, April 16, 1957.

with Herm, R. J. Incidence of Brushfield spots. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 23, 1957.

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Corneal dystrophy and degenerations. San Francisco Medical Society, in San Francisco, California, June 14, 1957.

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House Officer Lectures, Massachusetts Eye and Ear Infirmary

Corneal ulcers. February 13, 1957
Corneal dystrophy, I. March 5, 1957
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Systemic ophthalmology. April 30, 1957

GRANT, W. M.

Basic tonometry and tonography. Symposium on Glaucoma, 7th Annual Session of the New Orleans Academy of Ophthalmology, in New Orleans, Louisiana, February 11, 1957.

Aqueous production and flow, physiologic and pathologic aspects. Symposium on Glaucoma, 7th Annual Session of the New Orleans Academy of Ophthalmology, in New Orleans, Louisiana, February 12, 1957.

Discussion: "The effect of succinylcholine on the extraocular striate muscles and on the intraocular pressure," F. J. Macri. 26th Annual Meeting of the Association for Research in Ophthalmology, in New York, New York, June 4, 1957.

Toxicology and tonography. Series of lectures to the Lancaster Courses in Ophthalmology, in Waterville, Maine, August 3, 5, and 6, 1957.

Ocular hydrodynamics (non-mathematical). Los Angeles Society of Ophthalmology and Otolaryngology, in Los Angeles, California, September 5, 1957.

Experimentation in relation to glaucoma. San Francisco Ophthalmological Round Table, in San Francisco, California, September 6, 1957.

Management of angle-closure glaucoma. Cook County Medical Association Conference, in Chicago, Illinois, October 10, 1957.

Management of secondary glaucoma. Cook County Medical Association Conference, in Chicago, Illinois, October 10, 1957.

Instruction in gonioscopy. New England Ophthalmological Society, in Boston, Massachusetts, December 21, 1957.

GRANT, W. M. (*continued*)

Toxicology and glaucoma. Series of lectures to Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 18, 19 and November 13, 1957.

Pharmacology of glaucoma. Harvard Medical School, Department of Pharmacology, in Boston, Massachusetts, December 21, 1957.

House Officer Lectures, Massachusetts Eye and Ear Infirmary

Current concepts of intraocular hydrodynamics, May 28, 1957
Aphakic, exfoliative and phakogenic glaucoma, August 8, 1957

HILL, K.

Eye anatomy. Series of twelve lectures to the Orthoptic Students, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, 1956–1957.

KERN, H. L.

The nature of the binding of several inorganic cations to the corneal stroma. Second Ophthalmic Biochemistry Conference, in Cambridge, Massachusetts, February 24, 1957.

KINOSHITA, J. H.

Chairman of the Second Ophthalmic Biochemistry Conference, in Cambridge, Massachusetts, February 23–24, 1957.

Discussion: "Insulin and the lens," T. G. Farkas and J. W. Patterson. 26th Annual Meeting of the Association for Research in Ophthalmology, in New York, New York, June 6, 1957.

Discussion: "On the occurrence of proteolytic enzymes in normal and cataractous lenses," E. A. Zeller and Anima Devi. 26th Annual Meeting of the Association for Research in Ophthalmology, in New York, New York, June 6, 1957.

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LANGHAM, M. E.

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TROTTER, R. R.

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Perimetry. Series of lectures to the Lancaster Courses in Ophthalmology, in Waterville, Maine, September 5–7, 1957.

with Chandler, P. A. and Grant, W. M. Series of lectures on glaucoma at the Cook County Graduate School of Medicine, in Chicago, Illinois, October 11–12, 1957.

FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

I Give and Bequeath to the Howe Laboratory of Ophthalmology .....Dollars to be Applied to the Uses of Said Laboratory.

Such bequests are managed by the Treasurer's Office of Harvard University, and the income is accredited to the Laboratory.